

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-742

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Patent Information
pursuant to 21 C.F.R. 314.53
for
NDA # 21-742

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: To Be Determined
- Active Ingredient(s): Nebivolol hydrochloride
- Strength(s): ~~2.5mg~~, 5mg, 10mg, ~~15mg~~
- Dosage Form: Nebivolol Tablets

U.S. Patent Number: 6,545,040

Expiration Date: 04/08/20

Type of Patent

1. Drug substance (Active Ingredient) X Y ___ N
2. Drug Product (Composition/Formulation) X Y ___ N
3. Method of Use X Y ___ N

U.S. Patent Number 6,545,040 covers methods of treating hypertension.

Name of Patent Owner: Janssen Pharmaceutica N.V.

U.S. Patent Agent: President of Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road,
Titusville, NJ 08560

Copy to:
Janssen Pharmaceutica N.V.
J&J Patent Law Department Beerse
Turnhoutseweg 30,
B-2340 Beerse, Belgium

U.S. Patent Number: 5,759,580

Expiration Date: 06/02/15

Type of Patent

1. Drug substance (Active Ingredient) __Y X N
2. Drug Product (Composition/Formulation) X Y __N
4. Method of Use __Y X N

Name of Patent Owner: Janssen Pharmaceutica N.V.

U.S. Patent Agent: President of Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road,
Titusville, NJ 08560

Copy to:
Janssen Pharmaceutica N.V.
J&J Patent Law Department Beerse
Turnhoutseweg 30,
B-2340 Beerse, Belgium

The undersigned declares that the above stated United States Patent Numbers 6,545,040 and 5,759,580 cover the composition, formulation and/or method of use of nebivolol hydrochloride. The product is the subject of the application for which approval is being sought.

Signed: James M. Joyce

Name: James M. Joyce

Date: March 31, 2004

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
		NDA NUMBER	
		21-742	
		NAME OF APPLICANT / NDA HOLDER	
		Bertek Pharmaceuticals Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME)			
To Be Determined			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
Nebivolol hydrochloride		_____, 2.5mg, 5mg, 10mg _____	
DOSAGE FORM			
Nebivolol Tablets			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.</p>			
<p>For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p>			
<p>FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</p>			
<p>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</p>			
1. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	
5,759,580		6/2/1998	
		c. Expiration Date of Patent	
		6/2/2015	
d. Name of Patent Owner		Address (of Patent Owner)	
Janssen Pharmaceutica N.V.		J&J Patent Law Department Beerse	
		Turnhoutseweg 30	
		City/State	
		B-2340 Beerse	
		ZIP Code	FAX Number (if available)
		Belgium	+32 14 60-5491
		Telephone Number	E-Mail Address (if available)
		+32 14 60-3547	patents@janbe.jnj.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
<input type="checkbox"/> President of Janssen Pharmaceutica, Inc.		1125 Trenton-Harbourton Road	
		City/State	
		Titusville, NJ	
		ZIP Code	FAX Number (if available)
		08560	1-609-730-2665
		Telephone Number	E-Mail Address (if available)
		1-609-730-4600	pmille2@janus.jnj.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
<input type="checkbox"/> Yes <input type="checkbox"/> No			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No
- 2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Dawn J. Beto

06-02-04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Dawn J. Beto, Esq.

Address

781 Chestnut Ridge Road

City/State

Morgantown, WV

ZIP Code

26504-4310

Telephone Number

304-599-2595

FAX Number (if available)

304-598-5408

E-Mail Address (if available)

dawn.beto@mylanlabs.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Bertek Pharmaceuticals Inc.
Form FDA 3542A

Nebivolol Tablets
NDA 21-742

ATTACHMENT 2

**SIGNED FORM FDA 3542A
PATENT 6,545,040**

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
		NDA NUMBER	
		21-742	
		NAME OF APPLICANT / NDA HOLDER	
		Bertek Pharmaceuticals Inc.	

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)	
To Be Determined	
ACTIVE INGREDIENT(S)	STRENGTH(S)
Nebivolol hydrochloride	2.5mg, 5mg, 10mg
DOSAGE FORM	
Nebivolol Tablets	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,545,040	4/8/2003	4/8/2020
d. Name of Patent Owner	Address (of Patent Owner)	
Janssen Pharmaceutica N.V.	J&J Patent Law Department Beerse Turnhoutseweg 30	
	City/State	
	B-2340 Beerse	
	ZIP Code	FAX Number (if available)
	Belgium	+32 14 60-5491
	Telephone Number	E-Mail Address (if available)
	+32 14 60-3547	patents@janbe.jnj.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	1125 Trenton-Harbourton Road	
	City/State	
	Titusville, NJ	
	ZIP Code	FAX Number (if available)
	08560	1-609-730-2665
	Telephone Number	E-Mail Address (if available)
	1-609-730-4600	pmille2@janus.jnj.com

President of Janssen Pharmaceutica, Inc.

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No
- 2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 2.7 If the patent referenced in 2.4 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 4.2 Patent Claim Number (as listed in the patent) 5 and 6 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

Claim 5 - The proposed labeling provides "TRADE NAME™ is indicated in the management of hypertension." Page 12, lines 235-236.

Claim 6 - The proposed labeling provides "TRADE NAME™ is indicated in the management of hypertension." Page 12, lines 235-236.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <div style="font-size: 2em; font-family: cursive; text-align: center;">Dawn Beto</div>	<p>Date Signed</p> <div style="font-size: 1.5em; text-align: center;">06-02-04</div>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<p><input type="checkbox"/> NDA Applicant/Holder</p> <p><input type="checkbox"/> Patent Owner</p>	<p><input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p> <p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
<p>Name Dawn J. Beto, Esq.</p>	
<p>Address 781 Chestnut Ridge Road</p>	<p>City/State Morgantown, WV</p>
<p>ZIP Code 26504-4310</p>	<p>Telephone Number 304-599-2595</p>
<p>FAX Number (if available) 304-598-5408</p>	<p>E-Mail Address (if available) dawn.beto@mylanlabs.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
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- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahm/fdahm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 21-742

SUPPL #

HFD # 110

Trade Name Bystolic

Generic Name nebivolol

Applicant Name Mylan Bertek

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years NMEs

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES ☐

NO ☐

Investigation #2

YES ☐

NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES ☐

NO ☐

Investigation #2

YES ☐

NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☐

If yes, explain:

Name of person completing form: Dan Brum

Title: RPM

Date: 12/11/07

Name of Office/Division Director signing form: Robert Temple, M.D.

Title: Office Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Dan Brum

12/11/2007 12:45:38 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-742 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 5/31/07 PDUFA Goal Date: 11/30/07

HFD-110 Trade and generic names/dosage form: TRADENAME (nebivolol) 2.5, 5, and 10 mg Tablets

Applicant: Mylan Bertek Therapeutic Class: Beta-Blockers

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☒ Yes. Please proceed to the next question.
☐ No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: hypertension

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
☒ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☒ Yes: Please proceed to Section A.
☐ No: Please check all that apply: ☐ Partial Waiver ☐ Deferred ☐ Completed

NOTE: More than one may apply: In the first cycle, we deferred pediatric studies. DCRP requests a full waiver this cycle.

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☒ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☒ There are safety concerns: We are recommending that the drug nebivolol be granted a pediatric waiver because of the concerns regarding its effect on sperm in animal studies. Moreover we have already approved Toprol XL as a beta blocker with labeling in children. There were clear changes in mice treated with nebivolol both in histology and in sperm counts. There were changes also in rats limited to changes in normal sperm counts. In rats after 13 weeks of treatment and a 4 week recovery period, there was residual and actually worsening of the incidence of sperm abnormalities. Given the potential risk for provoking changes in long-term fertility, we recommend that no pediatric study be performed.
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Page 3

This page was completed by:

{See appended electronic signature page}

Daniel Brum
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

Dan Brum
11/14/2007 09:23:36 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-742

Stamp Date: April 30, 3004

Action Date:

HFD-110

Trade and generic names/dosage form: Nebivolol Hydrochloride Tablets

Applicant: Bertek Pharmaceuticals

Therapeutic Class: 1011000, Beta blockers

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: Hypertension

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☒ No: Please check all that apply: ☐ Partial Waiver ☒ Deferred ☐ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval

☐ Formulation needed☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. <u>0</u>	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. <u>16</u>	Tanner Stage _____

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population☐ Disease/condition does not exist in children☐ Too few children with disease to study☐ There are safety concerns☒ Adult studies ready for approval☐ Formulation needed

Other: _____

Date studies are due (mm/dd/yy): July 7, 2007; agreement with Division on plan to study nebivolol in pediatric patients: January 7, 2005

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melissa Robb, HFD-110
Regulatory Health Project Manager

cc: NDA 21-742
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Melissa Robb

7/7/04 12:55:17 PM



April 15, 2004

Douglas Throckmorton, MD, Director
Division of Cardio-Renal Drug Products, HFD 110
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-742; NEBIVOLOL TABLETS — 2.5mg, 10mg —

Dear Dr. Throckmorton:

Pursuant to 21 CFR 314.50(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Bertek hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Act in connection with the application for the referenced product.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. B. Miller', with a stylized flourish at the end.

Andrea B. Miller, R.Ph., Esq.
Vice President
Regulatory Affairs

ABM/gjn

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

NEB305; NEB306; NEB321

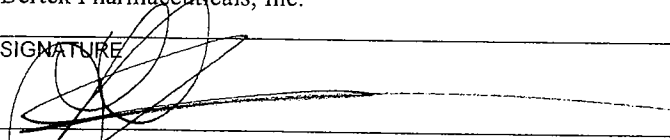
NEB202; NEB203; NEB302

Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	-----SEE ATTACHED LIST -----	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Leah L. Summers	TITLE Secretary, Bertek Pharmaceuticals, Inc.
FIRM / ORGANIZATION Bertek Pharmaceuticals, Inc.	
SIGNATURE 	DATE 4/12/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

63 Page(s) Withheld

6 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

Project Manager Overview
NDA 21-742
Nebivolol Tablets

Overview:

Bertek Pharmaceuticals submitted a New Drug Application (NDA) for nebivolol hydrochloride — 2.5, 5, 10, — mg tablets on April 30, 2004. The data submitted is to support an indication for the use of nebivolol in the management of hypertension when used alone or in combination with other antihypertensive agents. On May 31, 2007, the Agency received a Class 2 resubmission to address the deficiencies detailed in the approvable “AE” letter issued on May 31, 2005. In the resubmission, Mylan Bertek sought to market nebivolol 2.5, 5, and 10 mg tablets for the once-daily treatment of hypertension. On November 30, 2007, the Agency issues a second approvable letter citing a deficiency in the sponsor’s manufacturing site (Beerse facility). The sponsor’s December 5, 2007 submission constituted a Class I resubmission which included information related to the withdrawal of the Beerse manufacturing facility.

Office Director’s Memos

Dr. Robert Temple (3rd cycle)

Dr. Temple recommends approval.

Dr. Robert Temple (2nd cycle)

Dr. Temple recommends approval pending the resolution of the withhold status on the Beerse manufacturing facility.

Dr. Robert Temple; June 21, 2005

Dr. Temple supported an approvable action for this NDA due to concerns of the striking increase in leydig cell tumors in mice. He also discusses issues surrounding cardioselectivity, metabolites, racial and other subset differences in response, and adverse events.

Division Director’s Memos

Dr. Norman Stockbridge (3rd cycle)

Dr. Stockbridge recommends approval.

Dr. Norman Stockbridge (2nd cycle)

Dr. Stockbridge recommends approval pending the resolution of the withhold status on the sponsor’s manufacturing site. On November 30, 2007, the sponsor confirmed their plans to conduct a postmarketing placebo-controlled withdrawal study following at least three months of treatment.

Dr. Norman Stockbridge; May 9, 2005

Dr. Stockbridge supported an approvable action for this NDA and briefly discusses efficacy results and issues of concern.

Medical Reviews (primary and secondary)

Secondary Reviews

Dr. Abraham Karkowsky; November 17, 2007

Dr. Karkowsky recommends approval assuming the cGMP inspection report is satisfactory. In his review, he states that the sponsor adequately dealt with the question of Leydig cell tumors in male mice although other aspects of changes to the rodent reproductive system (e.g., reproductive and gonadic related effects) may be considered in the labeling.

Dr. Karkowsky recommends that the drug nebivolol be granted a pediatric waiver because of the concerns regarding its effect on sperm in animal studies. Moreover, DCRP has already approved Toprol XL as a beta blocker with labeling in children. There were clear changes in mice treated with nebivolol both in histology and in sperm counts. There were changes also in rats limited to changes in normal sperm counts. In rats after 13 weeks of treatment and a 4 week recovery period, there was residual and actually worsening of the incidence of sperm abnormalities.

Dr. Abraham Karkowsky; February 23, 2005

Dr. Karkowsky outlined the rationale for an approvable recommendation for Nebivolol Tablets for the treatment of hypertension. In his review, he states that there is sufficient information to ensure that nebivolol at a dose range of _____ to 40 mg once daily is effective in the treatment of essential hypertension. In addition, he stated that there is adequate information that nebivolol is useful for the treatment of hypertension in both Caucasian and black patients. However, Dr. Karkowsky stated that an approval recommendation will be dependant on demonstrating that the Leydig cell tumors observed in male mice at a dose of 40 mg/kg are not a relevant risk to humans.

Primary Reviews

Dr. Karen Hicks; October 19, 2007

Dr. Hicks recommends approval of nebivolol for the treatment of _____ hypertension.

The Agency's May 31, 2005 Action Letter indicated nebivolol was "Approvable" if the sponsor could establish the mechanism by which nebivolol was responsible for these findings in male mice, prove that the findings were not relevant in humans, and demonstrate nebivolol treatment did not alter adrenal function, LH, or testosterone levels in human males. The sponsor completed Studies NEB-TX-02 and NEB-PK-03 which were designed with input from the Agency.

NEB-PK-03 was a randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. The findings suggest that the Leydig cell tumors in male mice are species specific.

Since the safety review does not provide definitive evidence of hormonally mediated -- adverse events, it appears the preclinical findings are not likely to be relevant in humans. Per the Division of Metabolism and Endocrinology Products, based on the results of NEB-PK-03, "nebivolol is unlikely to cause clinically significant adrenal insufficiency with long-term use at the 10 mg dose in patients with baseline normal adrenal function." However, per DRUP, "without data from long-term studies, significant effects or lack of effects on gonadal function remain conjectural."

There are no required Phase 4 Commitments. However, the sponsor has 2 studies, NEB-310 and NEB-324, which are currently in progress. The sponsor should ensure that the following studies are completed and the Clinical Study Reports submitted for review.

Dr. Hicks concludes that the financial disclosure information submitted for studies NEB-PK-03, NEB-323, NEBI-0398, and NEBI-0438 is acceptable.

Dr. Karen Hicks, Dr. Juan Carlos Pelayo, Dr. Katherine Lille, Dr. Maryann Gordon, and Dr. Shari Targum; April 22, 2005

This review was of all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the pivotal studies. Per Dr. Hicks, this review is identical to the review dated April 11, 2005 with minor editorial changes. Therefore, only this copy is included in the action package.

Dr. Karen Hicks, Dr. Juan Carlos Pelayo, Dr. Katherine Lille, Dr. Maryann Gordon, and Dr. Shari Targum; April 11, 2005

NOTE: This review was revised and is dated April 22, 2005. This version is not included in the action package.

This review was of all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the pivotal studies.

Dr. Salma Lemtouni; March 10, 2005

In her review of safety, Dr. Lemtouni stated that the clinical program was designed to evaluate the efficacy of nebivolol and, as a result, was underpowered to assess the association of nebivolol with many of the adverse events observed. Dr. Lemtouni states that her conclusions drawn with regard to the safety of nebivolol rely on the comparison of safety results from the review of carvedilol, the labels of carvedilol and metoprolol succinate, and on the foreign post marketing data of nebivolol.

Dr. Lemtouni concluded that adverse events known to be associated with beta-adrenergic antagonism were experienced by subjects exposed to nebivolol as expected.

Abnormalities in liver function tests were observed with nebivolol as they were with carvedilol in hypertensive patients. Chest pain was experienced at a similar incidence as with metoprolol succinate in hypertensive patients. Dr. Lemtouni believed that Nebivolol may not be the only beta-blocker to be associated with potential angioedema because events of angioedema were reported in post marketing experience with many other beta-blockers. Therefore, the general experience of the nebivolol study population with regard

to study drug adverse effects was not different from that of the carvedilol and metoprolol hypertension study populations.

Dr. Lemtouni recommended including a warning in the label about potential angioedema.

Per Dr. Lemtouni, this review is an updated version of her previous review dated February 9, 2005 and is therefore the only version included in the action package.

Dr. Salma Lemtouni; February 9, 2005

NOTE: This review was revised by Dr. Lemtouni and is dated March 10, 2005. This version is not included in the action package.

In her review of safety, Dr. Lemtouni stated that the clinical program was designed to evaluate the efficacy of nebivolol and, as a result, was underpowered to assess the association of nebivolol with many of the adverse events observed. Dr. Lemtouni states that her conclusions drawn with regard to the safety of nebivolol rely on the comparison of safety results from the review of carvedilol, the labels of carvedilol and metoprolol succinate, and on the foreign post marketing data of nebivolol.

Dr. Lemtouni noted some issues that are of concern to her: nebivolol's potential myocardial ischemic effect, its lipid metabolism effects, its seemingly compromising effect of renal function, and its potential interaction with alcohol.

Dr. Karen Hicks; January 31, 2005

In her review of efficacy, Dr. Hicks stated that nebivolol is approvable for the treatment of: _____ hypertension, pending the following results:

1. The sponsor plans to perform mechanistic studies in mice and rats to explain the development of Leydig cell tumors (LCT). If the sponsor proves nebivolol is not potentially carcinogenic in humans, the application is approvable.
2. Through consultative review, the Division of Reproductive and Urologic Drug Products (DRUDP) will assist the Cardio-Renal Division in identifying the most sensitive markers for drug-related estrogenic effects in humans and in determining whether or not these markers predict the development of subsequent malignancies.

Dr. Hicks believes that based on the mouse carcinogenicity findings, nebivolol may be carcinogenic in humans. She stated that there is some nebivolol safety data covering approximately two years, but believes this time period does not adequately evaluate nor predict the malignant potential of this drug which would be taken chronically. In addition, Dr. Hicks states that it is unlikely post-marketing surveillance in Europe, where nebivolol has already been approved, would adequately record all malignancies in patients taking nebivolol.

Dr. Hicks states that the primary efficacy endpoint was the change in mean trough sitting diastolic blood pressure at the end of treatment compared to baseline. Nebivolol showed

statistically significant results at doses of 1.25 to 40 mg in NEB-302; 5, 10, and 20-mg-in NEB-305; and 5 to 40 mg in NEB-202. In addition, nebivolol had a statistically significant effect on most of the secondary endpoints.

In her review, Dr. Hicks stated that nebivolol is not significantly different from other β_1 selective blockers currently on the market, except that it is potentially carcinogenic in humans. Blacks require higher doses of nebivolol for efficacy, as they do with other beta blockers. Although *in vitro* experiments using human umbilical vein preparations and forearm blood flow studies in small numbers of humans suggest nebivolol may have some effect on nitric oxide release, the exact mechanism is unknown. Metoprolol, another β_1 selective adrenoceptor blocking agent, also increases nitric oxide release. Many of the studies were not placebo-controlled and were performed up to seventeen years ago. With technological improvements, it is unclear whether or not these results are reproducible today.

Dr. Hicks stated that risk management activities will be dependant on the findings of the mechanistic studies which the sponsor plans to perform and recommendations from the DRUDP.

Financial Disclosure: In her review, Dr. Hicks noted that the sponsor included Financial Certifications (FDA Form 3454) for the investigator's participating in NEB-302, NEB-305, NEB-202, NEB-306, NEB-203, and NEB-321. The sponsor stated that no investigator or sub-investigator had financial interest as described in 21 CFR 54 that required financial disclosure.

Labeling: Dr. Hicks stated in her review, that a labeling review is pending the Agency's final decision regarding approvability.

Clinical Inspections

November 2007: The inspector communicated deficiencies to Jansen, the manufacturer of the API. The Beerse facility in Belgium was given a Withhold recommendation.

In a review dated February 15, 2005, the Division of Scientific Investigation stated that no major deficiencies were noted in the three sites inspected that could compromise the integrity of the data and concluded that the data reviewed is acceptable. No subsequent actions or follow-up inspections were recommended. There were no limitations to the inspections.

Statistical Review

Ms. Jasmine Choi; December 17, 2004

Ms. Choi concluded in her review that nebivolol had a statistically significant effect on reducing sitting diastolic blood pressure not only in non-black patients, but also in black patients. The secondary analyses on other primary efficacy measurements confirmed that nebivolol had a statistically significant antihypertensive effect on mild to moderate hypertension population.

The primary analyses on general population (NEB-302 and NEB-305) showed that the sitting DBP of all dosed groups was significantly decreased compared to the placebo groups (NEB-302, $p < 0.0001$ for all doses; NEB-305, $p < 0.0015$). The same analysis on black population (NEB-202) showed a statistically significant reduction of sitting DBP in all dose groups, except the 2.5 mg dose group.

For the secondary analyses, change of sitting SBP at trough and rates of responder, which was defined as a patient whose average sitting DBP at trough was either $< 90 \text{ mmHg}$ at the end of treatment or had decreased by $\geq 10 \text{ mmHg}$ from baseline, were analyzed. The results of these secondary analyses confirmed the findings from the primary analyses.

Clinical Pharmacology and Biopharmaceutics Reviews

Dr. Elena Mishina; May 11, 2005

In her review, Dr. Mishina reviewed the sponsor's responses to the comments that were sent by the Division following the first clinical pharmacology and biopharmaceutics review. The following dissolution methods and specifications were recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	— in 30 minutes

Dr. Elena Mishina and Dr. Robert Kumi; January 31, 2005

In this review, Dr. Mishina and Dr. Kumi stated that the clinical pharmacology and biopharmaceutics sections are acceptable, provided that the labeling comments are adequately addressed. The biowaiver requested for the 2.5 mg dose was granted. In addition, the following dissolution methods and specifications were recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	— in 15 minutes

The following list of issues was not addressed by the sponsor:

1. The pharmacokinetics of the active metabolites of nebivolol was not assessed. This led to the inability to explain why the striking difference in pharmacokinetics of the parent drug in extensive and poor metabolizers of CYP2D6 did not show any differences in the drug effect.

2. The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.
3. The sponsor is requested to evaluate the PK/PD relationship in African-American hypertensive patients.

Labeling: Dr. Mishina and Dr. Kumi included labeling recommendations in their review.

Pharmacology Reviews

Dr. Elizabeth Hausner; November 1, 2007

In her review, Dr. Hausner discusses the results of each of the studies (see Summary and Discussion beginning on p. 62 of her review).

Dr. Elizabeth Hausner; November 1, 2007

Dr. Hausner requested consults from the Division of Metabolic and Endocrine Products and Biometrics and presents their comments and recommendations in this memo to file.

Dr. Elizabeth Hausner; November 1, 2007

In this review, Dr. Hausner evaluates historical control data for sperm parameters and concludes there appears to be a drug-related detrimental effect upon sperm count, motility and morphology in both rodent species but no detected effect on canine testes/sperm. She notes there was no statement as to the quality of the slides used for re-evaluation.

Dr. Elizabeth Hausner; April 11, 2005

This review was of a protocol change of the sponsor's mechanistic study which the sponsor had designed to provide support to their assertion that nebivolol did not pose a cancer risk to humans. The Division agreed with the sponsor's proposed change to the protocol and conveyed this information to them.

Dr. Elizabeth Hausner; April 11, 2005

This review was of summary tables of the incidences of the histological findings which were requested by the Division in order to clarify various references throughout the reports that indicated that the reproductive tract was one of the target organs of toxicity. Dr. Hausner stated that she is unable to come to a definitive interpretation of the data, but the data generates the overall impression that there is a signal to be investigated regarding a possible hormonal effect of nebivolol.

Dr. Elizabeth Hausner; March 24, 2005

This review was of material submitted from a DMF and was in response to the chemistry reviewer noting that there was an impurity to be qualified. The sponsor provided studies in support of the qualification of the impurity. Dr. Hausner stated that overall, the combination of impurities added to nebivolol did not cause any new effects compared to nebivolol alone. She stated that there is no discernible signal that this combination of impurities and nebivolol causes any appreciable biological effects.

Dr. Hausner noted in her review, that the sponsor stated that there is a drug-related effect on cyclicity seen at 14 days of dosing using a dose that has not produced clear effects after 6 months of dosing.

Dr. Elizabeth Hausner; February 24, 2005

This review covered material submitted by the sponsor in response to the Division's repeated requests for data to indicate that the reproductive toxicology findings were not of clinical relevance. Dr. Hausner concluded that this submission did adequately address the reproductive and developmental issues that concern the Division.

Dr. Elizabeth Hausner; January 24, 2005

In her review, Dr. Hausner stated that this application was approvable depending upon the clinical findings. Dr. Hausner recommended the following nonclinical studies, but added that at this stage there may be sufficient clinical data to resolve these issues without conducting further non-clinical testing: characterization of the active metabolites, possible bone marrow toxicity, endocrine disruption, and repolarization effects. Dr. Hausner concluded that there are a number of consistent features in the toxicology studies. She stated that the level of detail provided is sub-optimal, particularly with regard to histopathology results. In the majority of reports, summary incidence tables are lacking and a scoring system is used which she believes to some extent makes interpretation difficult. Dr. Hausner added that detailed verbal descriptions of histopathology findings are almost entirely lacking. Similar comments could be made about some of the safety pharmacology studies where raw or interpretable results were not presented and scoring systems were used, making independent interpretation difficult. Dr. Hausner noted that reproductive toxicology was apparent. Dr. Hausner noted the following unresolved toxicology issues:

1. N122168 Micronucleus test in mice: single oral dose. Single oral doses of nebivolol in male and female mice showed significant ($p \leq 0.05-0.001$) and dose-related reduction in bone marrow proliferation at the 24 hour sampling time. This bone marrow toxicity was not examined or at least there was no information in the toxicology reports characterizing or further exploring this finding. Decreases in HCT, Hb and RBC were seen in the hematology results of most toxicology studies. Enlarged spleens with increased RBC in the pulp were reported for most studies, even in situations where hematology changes were not apparent. The findings are more consistent with a hemolytic anemia rather than bone marrow depression. Dr. Hausner was unsure if the original observation was a random fluke, as one would think that if the observation was real, that there might have been some clinical evidence to corroborate this finding by now. The points which should have been characterized include:
 - a. Did the original effect repeat?
 - b. A NOAEL for the bone marrow toxicity
 - c. Is the effect reversible, progressive or self-limiting?
2. QTc prolongation. This appeared inconsistently. A consistent feature of the QTc evaluation was the lack of detail as to the determination of ECG collection

relative to dosing. Also, Bazett's formula appeared to be the only method of correction used, even though it was inappropriate given the heart rates of the dogs. In the acute cardiovascular safety study, there were no apparent effects on QTc. A 2-week, repeat dose study in dogs also showed no QTc effects. A one-month, oral dosing study showed QTc increased in all groups including controls. One month of intravenous dosing showed a decrease in QTc values. A 3-month, oral study showed inconsistent QTc increases from week 4 onward. A HERG assay indicated that nebivolol inhibits the IKr channel with an $IC_{50} = 3 \times 10^{-7} M$ compared to astemizole, $IC_{50} = 2 \times 10^{-8} M$ in the same assay.

3. Endocrine disruption. This conclusion of endocrine disruption is due to several points of data:
 - a. Dose-related increase in Leydig cell tumors (LCT) in mice. The LCT were assessed by the Executive CAC to be drug-related. LCT in mice are typically due to an estrogen receptor mechanism.
 - b. Several toxicology studies report weight effects in the reproductive organs of both sexes. Gross and histologic changes were also noted in report texts, but detailed descriptions and incidences were not provided. For the female reproductive tract, the sponsor notes "a more resting aspect in the female genital tract" as well as fewer corpora lutea and more atretic follicles. Changes in the male reproductive organs were noted in the 3-month study in mice and included Leydig cell hyperplasia (160 mg/kg), large nucleated tubular cells and testicular atrophy due to delayed maturation. Rat studies showed increased gonad weight (no detail as to the specifics). The 6-month rat study reported a decrease in gonad weight and testicular degenerative changes with low numbers of spermatozoa and "possible cellular debris in the epididymus." The one-month dog study showed an increase in male prostate weight and no histopath information. The 3-month dog study showed increased gonad weight at 2.5, 10 and 40 mg/kg with urolithiasis at the LD and prostatitis at the MD.

Labeling: Dr. Hausner included labeling recommendations in her review.

Dr. Elizabeth Hausner; January 4, 2005

This review was of the sponsor's November 12, 2004 submission which included 6 studies for review. Two studies were reviewed. In her review of XBL study # 04683, XBL report #RPT01128 *In vitro* Metabolism of [^{14}C]-Nebivolol in Liver Microsomes, and Liver s9 Fraction from Mouse, Rat, Dog, and Human, Dr. Hausner concluded that overall, the *in vitro* metabolic profiles of [^{14}C]-d and [^{14}C]-l-nebivolol were qualitatively similar. In her review of XBL study #04685, XBL report #RPT01174 Search and Investigation of Nebivolol Metabolites in Plasma Samples from Human, Rat, Mouse, and Dog using Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) techniques, Dr. Hausner stated that the study was initiated several months into the NDA review and completed late in the review cycle. Dr. Hausner stated that this material does not substantially alter the overall non-clinical picture of nebivolol.

Dr. Elizabeth Hausner; December 30, 2004

This review was of the sponsor's November 23, 2004 submission which was a follow-up to a teleconference between the Division and the sponsor in September 2004 when the sponsor was notified that the Executive CAC had determined that the Leydig cell tumors present in mice were drug related. At that teleconference, the sponsor was asked to make a case that this finding was not clinically relevant. This submission included a reevaluation of the slides in a "blinded" fashion and a report from the Pathology Working Group which was assembled after the reread. Dr. Hausner stated that the submission did not change the conclusion of the tumorigenic potential of the drug and the material presented did not address the Division's question as to the relevance of this finding in humans.

Statistical Review of Carcinogenicity

Ms. Jasmine Choi; July 22, 2004

Ms. Choi reviewed two carcinogenicity studies, a two year rat study (Study 1968) and an 18 month mouse study (Study 1967). Ms. Choi noted that in the rat study the dose-mortality trend tests and homogeneity test for both genders showed no statistically significant treatment effect on survival and that the study had been extended until 50% mortality was reached. Ms. Choi concluded that based on the statistical criteria there were a sufficient number of rats living long enough to present late developing tumors and the high dose reached the MTD. Ms. Choi stated that in the mouse study the treatment did not effect the survival of either gender. Leydig cell tumors in the testis showed a statistically significant trend in males. There were no other tumors with a positive dose-related trend. The validity of the study was evaluated since there were no significant tumor findings in females. Ms. Choi stated that the evaluation suggested that enough numbers of animals were at risk for a sufficient length of time, but that the high dose did not reach the MTD.

Executive CAC Report from meeting on August 24, 2004

The committee found the rat and mouse studies were adequate. The Leydig cell tumors seen in male mice were considered drug-related. The committee also stated that because of the possibility of body weight effects in the rat study altering the tumor incidence in the HD groups, it was requested that the mammary tumors be reanalyzed omitting the HD group. The reanalysis consisted of a trend test comparing the vehicle control, LD and MD groups but omitting the HD group. Benign (adenomatous) neoplasia was to be analyzed separately from carcinoma/sarcoma neoplasms. A combination of all mammary tumors would then also be analyzed. The rat study was found to be negative for carcinogenicity when associated tumor types were analyzed separately. When mammary neoplasms were reanalyzed in accordance with the recommendations of the committee, neither trend tests (vehicle control, LD, and MD) nor pairwise comparisons (vehicle control vs MD) resulted in statistically significant findings.

Chemistry Reviews

Dr. Ramsharan Mittal; December 13, 2007

In his sixth review, Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance and all other pending CMC issues have been resolved. Finally, the application may be approved from a chemistry standpoint.

Dr. Ramsharan Mittal; November 30, 2007

Dr. Mittal recommends approvable from a CMC perspective because of the withhold status of drug substance manufacturing site at Janssen Pharmaceutica N V, Beerse, BE.

Dr. Ramsharan Mittal; November 1, 2007

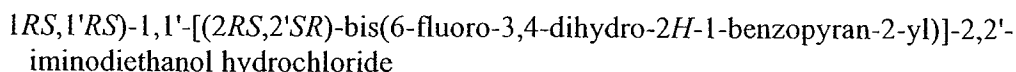
Dr. Mittal recommends approval if the pending cGMP inspection of the Jansen manufacturing facility is deemed acceptable. In sum, an expiration date of 36 months is acceptable and Dr. Mittal's recommendations have been incorporated in the draft labeling.

Dr. Ramsharan Mittal; April 29, 2005

Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of — months is acceptable for Nebivolol Tablets packaged in — bottles of —30, 100 and — tablets and unit-dose

— . In addition, the deficiencies noted in earlier CMC reviews have been satisfactorily addressed by the sponsor and the application can be approved from a chemistry perspective.

Dr. Mittal states that the sponsor should be informed to use the following recently approved nebivolol hydrochloride USAN chemical name in the package insert, which should be included in marked up labeling:



Dr. Mittal also noted that the Office of Clinical Pharmacology and Biopharmaceutics review is still pending.

Dr. Ramsharan Mittal; March 11, 2005

Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of — months is acceptable for Nebivolol Tablets packaged in — bottles of —30, 100 — tablets and unit-dose

— . However, Dr. Mittal states that the chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the Nebivolol 2.5, 5, and 10 mg Tablets. The application is approvable from chemistry perspective pending resolution of these deficiencies.

Dr. Mittal had the following comments for the sponsor:

1. Regarding water and identification specifications of Nebivolol Hydrochloride Tablets

The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about —. The proposed limit for water content of — is too high and should be Not More Than —. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Regarding in-process blend uniformity testing

Please note that mere generation of acceptable data from a number of batches will not be considered a sufficient justification for deletion of in-process blend uniformity testing.

3. Regarding Post-approval Stability Protocols of Nebivolol Hydrochloride Tablets

The post approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on post approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations and should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

4. Regarding labeling issues of the drug product Nebivolol Hydrochloride Tablets

Please submit a request for a USAN for (±) nebivolol hydrochloride and provide a copy of the USAN request to this NDA as a part of your response. Please note that the current USP

Dictionary lists only nebivolol free base with inadequate structure representation since no stereochemistry is shown.

Dr. Ramsharan Mittal; February 15, 2005

Dr. Mittal states that the Chemistry Manufacturing and Controls information in this application was provided for different dose strengths — 2.5, 5, 10, — mg. The sponsor is marketing _____ dose strengths 2.5, 5, and 10 mg. _____

—

In his review, Dr. Mittal states that the chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the nebivolol 2.5, 5, and 10 mg Tablets. Dr. Mittal states the following deficiencies should be included in the action letter:

1. Regarding water and identification specifications of Nebivolol Hydrochloride tablets.

The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about —. The proposed limit for water content of — is too high and should be Not More Than —. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Regarding in-process blend uniformity testing.

Please note that mere generation of acceptable data from a number of batches will not be considered a sufficient justification for deletion of in-process blend uniformity testing.

3. Regarding Post-approval Stability Protocols of Nebivolol Hydrochloride Tablets.

The post approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on post approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations and should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

4. Regarding labeling issues of the drug product Nebivolol Hydrochloride Tablets.

NEBIVOLOL HCL

Based on the submitted stability data, an expiration date of 36 months is acceptable for nebivolol tablets packaged in 30, 100, 300 tablets and unit-dose

Dr. Mittal stated that a final recommendation on approvability of Nebivolol Hydrochloride 2.5, 5, and 10 mg Tablets can not be given at this time since an overall recommendation from the Office of Compliance is pending because cGMP inspection of

the drug substance manufacturing facilities (Jansen Pharmaceuticals) has not been completed and the facilities are scheduled to be inspected between February 6 – 16, 2005.

EES: Pending, due to be completed February 16, 2004

Methods of Validation: To be submitted after NDA approval

Labeling: Dr. Mittal included labeling recommendations in his review.

Categorical Exclusion from the Environmental Assessment: Acceptable

DDMAC Reviews

In a review dated October 29, 2007, DDMAC reviewed the proposed package insert (from October 27, 2007). DDMAC offered recommendations to the Clinical Pharmacology, Clinical Studies, Warnings, Precautions, and Adverse Reactions sections of the PI.

In a review dated March 10, 2005, DDMAC reviewed the sponsor's rebuttal to DDMAC's objection to the use of the tradename " ——— ". DDMAC stated that they continue to consider the tradename overly fanciful and overstating the efficacy of nebivolol.

In a review dated February 9, 2005, DDMAC provided comments on the sponsor's proposed package insert.

DMETS Reviews

DMETS; November 16, 2007

In a review dated November 16, 2007, DMETS concurred with DDMAC to NOT recommend the use of the proprietary name " ——— " based on promotional concerns.

DMETS; October 18, 2007

In a review dated October 18, 2007, DMETS did NOT recommend the use of the proprietary name Cirmaxen. DDMAC found Cirmaxen to be acceptable from a promotional perspective. In November, the sponsor submitted three more tradenames for DMETS to consider including " ——— " 2) Bystolic, and " ——— ".

DMETS; February 3, 2005

In a review dated February 3, 2005, DMETS did not recommend the use of the proprietary name " ——— " and commented also that DDMAC did not recommend the use of " ——— " from a promotional perspective.

DMETS; August 11, 2004

In a review dated August 11, 2004, DMETS provided comments on the sponsor's original draft labels and labeling submitted by the sponsor without a proprietary name. DMETS requested final printed labeling be submitted for review when available.

ACTION:

An approval (AP) letter has been drafted for Dr. Temple's review.

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/s/

Dan Brum
12/17/2007 06:17:42 PM
CSO

Project Manager Overview
NDA 21-742
Nebivolol Tablets

Overview:

Bertek Pharmaceuticals submitted a New Drug Application (NDA) for nebivolol hydrochloride — 2.5, 5, 10, — mg tablets on April 30, 2004. The data submitted is to support an indication for the use of nebivolol in the management of hypertension when used alone or in combination with other antihypertensive agents. On May 31, 2007, the Agency received a Class 2 resubmission to address the deficiencies detailed in the approvable "AE" letter issued on May 31, 2005. In the resubmission, Mylan Bertek seeks to market nebivolol 2.5, 5, and 10 mg tablets for the once-daily treatment of hypertension.

Office Director's Memos

Dr. Robert Temple (2nd cycle)

Dr. Temple recommends approval pending the resolution of the withhold status on the Beerse manufacturing facility.

Dr. Robert Temple; June 21, 2005

Dr. Temple supported an approvable action for this NDA due to concerns of the striking increase in leydig cell tumors in mice. He also discusses issues surrounding cardioselectivity, metabolites, racial and other subset differences in response, and adverse events.

Division Director's Memos

Dr. Norman Stockbridge (2nd cycle)

Dr. Stockbridge recommends approval pending the resolution of the withhold status on the sponsor's manufacturing site. On November 30, 2007, the sponsor confirmed their plans to conduct a postmarketing placebo-controlled withdrawal study following at least three months of treatment.

Dr. Norman Stockbridge; May 9, 2005

Dr. Stockbridge supported an approvable action for this NDA and briefly discusses efficacy results and issues of concern.

Medical Reviews (primary and secondary)

Secondary Reviews

Dr. Abraham Karkowsky; November 17, 2007

Dr. Karkowsky recommends approval assuming the cGMP inspection report is satisfactory. In his review, he states that the sponsor adequately dealt with the question of Leydig cell tumors in male mice although other aspects of changes to the rodent reproductive system (e.g., reproductive and gonadal related effects) may be considered in the labeling.

Dr. Karkowsky recommends that the drug nebivolol be granted a pediatric waiver because of the concerns regarding its effect on sperm in animal studies. Moreover, DCRP has already approved Toprol XL as a beta blocker with labeling in children. There were clear changes in mice treated with nebivolol both in histology and in sperm counts. There were changes also in rats limited to changes in normal sperm counts. In rats after 13 weeks of treatment and a 4 week recovery period, there was residual and actually worsening of the incidence of sperm abnormalities.

Dr. Abraham Karkowsky; February 23, 2005

Dr. Karkowsky outlined the rationale for an approvable recommendation for Nebivolol Tablets for the treatment of hypertension. In his review, he states that there is sufficient information to ensure that nebivolol at a dose range of _____ to 40 mg once daily is effective in the treatment of essential hypertension. In addition, he stated that there is adequate information that nebivolol is useful for the treatment of hypertension in both Caucasian and black patients. However, Dr. Karkowsky stated that an approval recommendation will be dependant on demonstrating that the Leydig cell tumors observed in male mice at a dose of 40 mg/kg are not a relevant risk to humans.

Primary Reviews

Dr. Karen Hicks; October 19, 2007

Dr. Hicks recommends approval of nebivolol for the treatment of _____ hypertension.

The Agency's May 31, 2005 Action Letter indicated nebivolol was "Approvable" if the sponsor could establish the mechanism by which nebivolol was responsible for these findings in male mice, prove that the findings were not relevant in humans, and demonstrate nebivolol treatment did not alter adrenal function, LH, or testosterone levels in human males. The sponsor completed Studies NEB-TX-02 and NEB-PK-03 which were designed with input from the Agency.

NEB-PK-03 was a randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. The findings suggest that the Leydig cell tumors in male mice are species specific.

Since the safety review does not provide definitive evidence of hormonally mediated adverse events, it appears the preclinical findings are not likely to be relevant in humans. Per the Division of Metabolism and Endocrinology Products, based on the results of NEB-PK-03, "nebivolol is unlikely to cause clinically significant adrenal insufficiency with long-term use at the 10 mg dose in patients with baseline normal adrenal function." However, per DRUP, "without data from long-term studies, significant effects or lack of effects on gonadal function remain conjectural."

There are no required Phase 4 Commitments. However, the sponsor has 2 studies, NEB-310 and NEB-324, which are currently in progress. The sponsor should ensure that the following studies are completed and the Clinical Study Reports submitted for review.

Dr. Hicks concludes that the financial disclosure information submitted for studies NEB-PK-03, NEB-323, NEBI-0398, and NEBI-0438 is acceptable.

Dr. Karen Hicks, Dr. Juan Carlos Pelayo, Dr. Katherine Lille, Dr. Maryann Gordon, and Dr. Shari Targum; April 22, 2005

This review was of all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the pivotal studies. Per Dr. Hicks, this review is identical to the review dated April 11, 2005 with minor editorial changes. Therefore, only this copy is included in the action package.

Dr. Karen Hicks, Dr. Juan Carlos Pelayo, Dr. Katherine Lille, Dr. Maryann Gordon, and Dr. Shari Targum; April 11, 2005

NOTE: This review was revised and is dated April 22, 2005. This version is not included in the action package.

This review was of all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the pivotal studies.

Dr. Salma Lemtouni; March 10, 2005

In her review of safety, Dr. Lemtouni stated that the clinical program was designed to evaluate the efficacy of nebivolol and, as a result, was underpowered to assess the association of nebivolol with many of the adverse events observed. Dr. Lemtouni states that her conclusions drawn with regard to the safety of nebivolol rely on the comparison of safety results from the review of carvedilol, the labels of carvedilol and metoprolol succinate, and on the foreign post marketing data of nebivolol.

Dr. Lemtouni concluded that adverse events known to be associated with beta-adrenergic antagonism were experienced by subjects exposed to nebivolol as expected. Abnormalities in liver function tests were observed with nebivolol as they were with carvedilol in hypertensive patients. Chest pain was experienced at a similar incidence as with metoprolol succinate in hypertensive patients. Dr. Lemtouni believed that Nebivolol may not be the only beta-blocker to be associated with potential angioedema because events of angioedema were reported in post marketing experience with many other beta-blockers. Therefore, the general experience of the nebivolol study population with regard to study drug adverse effects was not different from that of the carvedilol and metoprolol hypertension study populations.

Dr. Lemtouni recommended including a warning in the label about potential angioedema.

Per Dr. Lemtouni, this review is an updated version of her previous review dated February 9, 2005 and is therefore the only version included in the action package.

Dr. Salma Lemtouni; February 9, 2005

NOTE: This review was revised by Dr. Lemtouni and is dated March 10, 2005. This version is not included in the action package.

In her review of safety, Dr. Lemtouni stated that the clinical program was designed to evaluate the efficacy of nebivolol and, as a result, was underpowered to assess the association of nebivolol with many of the adverse events observed. Dr. Lemtouni states that her conclusions drawn with regard to the safety of nebivolol rely on the comparison of safety results from the review of carvedilol, the labels of carvedilol and metoprolol succinate, and on the foreign post marketing data of nebivolol.

Dr. Lemtouni noted some issues that are of concern to her: nebivolol's potential myocardial ischemic effect, its lipid metabolism effects, its seemingly compromising effect of renal function, and its potential interaction with alcohol.

Dr. Karen Hicks; January 31, 2005

In her review of efficacy, Dr. Hicks stated that nebivolol is approvable for the treatment of _____ hypertension, pending the following results:

1. The sponsor plans to perform mechanistic studies in mice and rats to explain the development of Leydig cell tumors (LCT). If the sponsor proves nebivolol is not potentially carcinogenic in humans, the application is approvable.
2. Through consultative review, the Division of Reproductive and Urologic Drug Products (DRUDP) will assist the Cardio-Renal Division in identifying the most sensitive markers for drug-related estrogenic effects in humans and in determining whether or not these markers predict the development of subsequent malignancies.

Dr. Hicks believes that based on the mouse carcinogenicity findings, nebivolol may be carcinogenic in humans. She stated that there is some nebivolol safety data covering approximately two years, but believes this time period does not adequately evaluate nor predict the malignant potential of this drug which would be taken chronically. In addition, Dr. Hicks states that it is unlikely post-marketing surveillance in Europe, where nebivolol has already been approved, would adequately record all malignancies in patients taking nebivolol.

Dr. Hicks states that the primary efficacy endpoint was the change in mean trough sitting diastolic blood pressure at the end of treatment compared to baseline. Nebivolol showed statistically significant results at doses of 1.25 to 40 mg in NEB-302; 5, 10, and 20 mg in NEB-305; and 5 to 40 mg in NEB-202. In addition, nebivolol had a statistically significant effect on most of the secondary endpoints.

In her review, Dr. Hicks stated that nebivolol is not significantly different from other β_1 selective blockers currently on the market, except that it is potentially carcinogenic in humans. Blacks require higher doses of nebivolol for efficacy, as they do with other beta blockers. Although *in vitro* experiments using human umbilical vein preparations and forearm blood flow studies in small numbers of humans suggest nebivolol may have some effect on nitric oxide release, the exact mechanism is unknown. Metoprolol, another β_1 selective adrenoceptor blocking agent, also increases nitric oxide release.

Many of the studies were not placebo-controlled and were performed up to seventeen years ago. With technological improvements, it is unclear whether or not these results are reproducible today.

Dr. Hicks stated that risk management activities will be dependant on the findings of the mechanistic studies which the sponsor plans to perform and recommendations from the DRUDP.

Financial Disclosure: In her review, Dr. Hicks noted that the sponsor included Financial Certifications (FDA Form 3454) for the investigator's participating in NEB-302, NEB-305, NEB-202, NEB-306, NEB-203, and NEB-321. The sponsor stated that no investigator or sub-investigator had financial interest as described in 21 CFR 54 that required financial disclosure.

Labeling: Dr. Hicks stated in her review, that a labeling review is pending the Agency's final decision regarding approvability.

Clinical Inspections

November 2007: The inspector communicated deficiencies to Jansen, the manufacturer of the API. The Beerse facility in Belgium was given a Withhold recommendation.

In a review dated February 15, 2005, the Division of Scientific Investigation stated that no major deficiencies were noted in the three sites inspected that could compromise the integrity of the data and concluded that the data reviewed is acceptable. No subsequent actions or follow-up inspections were recommended. There were no limitations to the inspections.

Statistical Review

Ms. Jasmine Choi; December 17, 2004

Ms. Choi concluded in her review that nebivolol had a statistically significant effect on reducing sitting diastolic blood pressure not only in non-black patients, but also in black patients. The secondary analyses on other primary efficacy measurements confirmed that nebivolol had a statistically significant antihypertensive effect on mild to moderate hypertension population.

The primary analyses on general population (NEB-302 and NEB-305) showed that the sitting DBP of all dosed groups was significantly decreased compared to the placebo groups (NEB-302, $p < 0.0001$ for all doses; NEB-305, $p < 0.0015$). The same analysis on black population (NEB-202) showed a statistically significant reduction of sitting DBP in all dose groups, except the 2.5 mg dose group.

For the secondary analyses, change of sitting SBP at trough and rates of responder, which was defined as a patient whose average sitting DBP at trough was either $< 90 \text{ mmHg}$ at the end of treatment or had decreased by $\geq 10 \text{ mmHg}$ from baseline, were analyzed. The results of these secondary analyses confirmed the findings from the primary analyses.

Clinical Pharmacology and Biopharmaceutics Reviews

Dr. Elena Mishina; May 11, 2005

In her review, Dr. Mishina reviewed the sponsor's responses to the comments that were sent by the Division following the first clinical pharmacology and biopharmaceutics review. The following dissolution methods and specifications were recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	— in 30 minutes

Dr. Elena Mishina and Dr. Robert Kumi; January 31, 2005

In this review, Dr. Mishina and Dr. Kumi stated that the clinical pharmacology and biopharmaceutics sections are acceptable, provided that the labeling comments are adequately addressed. The biowaiver requested for the 2.5 mg dose was granted. In addition, the following dissolution methods and specifications were recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	— in 15 minutes

The following list of issues was not addressed by the sponsor:

1. The pharmacokinetics of the active metabolites of nebivolol was not assessed. This led to the inability to explain why the striking difference in pharmacokinetics of the parent drug in extensive and poor metabolizers of CYP2D6 did not show any differences in the drug effect.
2. The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.
3. The sponsor is requested to evaluate the PK/PD relationship in African-American hypertensive patients.

Labeling: Dr. Mishina and Dr. Kumi included labeling recommendations in their review.

Pharmacology Reviews

Dr. Elizabeth Hausner; November 1, 2007

In her review, Dr. Hausner discusses the results of each of the studies (see Summary and Discussion beginning on p. 62 of her review).

Dr. Elizabeth Hausner; November 1, 2007

Dr. Hausner requested consults from the Division of Metabolic and Endocrine Products and Biometrics and presents their comments and recommendations in this memo to file.

Dr. Elizabeth Hausner; November 1, 2007

In this review, Dr. Hausner evaluates historical control data for sperm parameters and concludes there appears to be a drug-related detrimental effect upon sperm count, motility and morphology in both rodent species but no detected effect on canine testes/sperm. She notes there was no statement as to the quality of the slides used for re-evaluation.

Dr. Elizabeth Hausner; April 11, 2005

This review was of a protocol change of the sponsor's mechanistic study which the sponsor had designed to provide support to their assertion that nebivolol did not pose a cancer risk to humans. The Division agreed with the sponsor's proposed change to the protocol and conveyed this information to them.

Dr. Elizabeth Hausner; April 11, 2005

This review was of summary tables of the incidences of the histological findings which were requested by the Division in order to clarify various references throughout the reports that indicated that the reproductive tract was one of the target organs of toxicity. Dr. Hausner stated that she is unable to come to a definitive interpretation of the data, but the data generates the overall impression that there is a signal to be investigated regarding a possible hormonal effect of nebivolol.

Dr. Elizabeth Hausner; March 24, 2005

This review was of material submitted from a DMF and was in response to the chemistry reviewer noting that there was an impurity to be qualified. The sponsor provided studies in support of the qualification of the impurity. Dr. Hausner stated that overall, the combination of impurities added to nebivolol did not cause any new effects compared to nebivolol alone. She stated that there is no discernible signal that this combination of impurities and nebivolol causes any appreciable biological effects.

Dr. Hausner noted in her review, that the sponsor stated that there is a drug-related effect on cyclicity seen at 14 days of dosing using a dose that has not produced clear effects after 6 months of dosing.

Dr. Elizabeth Hausner; February 24, 2005

This review covered material submitted by the sponsor in response to the Division's repeated requests for data to indicate that the reproductive toxicology findings were not of clinical relevance. Dr. Hausner concluded that this submission did adequately address the reproductive and developmental issues that concern the Division.

Dr. Elizabeth Hausner; January 24, 2005

In her review, Dr. Hausner stated that this application was approvable depending upon the clinical findings. Dr. Hausner recommended the following nonclinical studies, but added that at this stage there may be sufficient clinical data to resolve these issues without conducting further non-clinical testing: characterization of the active metabolites, possible bone marrow toxicity, endocrine disruption, and repolarization effects. Dr. Hausner concluded that there are a number of consistent features in the toxicology studies. She stated that the level of detail provided is sub-optimal, particularly with regard to histopathology results. In the majority of reports, summary incidence tables are lacking and a scoring system is used which she believes to some extent makes interpretation difficult. Dr. Hausner added that detailed verbal descriptions of histopathology findings are almost entirely lacking. Similar comments could be made about some of the safety pharmacology studies where raw or interpretable results were not presented and scoring systems were used, making independent interpretation difficult. Dr. Hausner noted that reproductive toxicology was apparent. Dr. Hausner noted the following unresolved toxicology issues:

1. N122168 Micronucleus test in mice: single oral dose. Single oral doses of nebivolol in male and female mice showed significant ($p \leq 0.05-0.001$) and dose-related reduction in bone marrow proliferation at the 24 hour sampling time. This bone marrow toxicity was not examined or at least there was no information in the toxicology reports characterizing or further exploring this finding. Decreases in HCT, Hb and RBC were seen in the hematology results of most toxicology studies. Enlarged spleens with increased RBC in the pulp were reported for most studies, even in situations where hematology changes were not apparent. The findings are more consistent with a hemolytic anemia rather than bone marrow depression. Dr. Hausner was unsure if the original observation was a random fluke, as one would think that if the observation was real, that there might have been some clinical evidence to corroborate this finding by now. The points which should have been characterized include:
 - a. Did the original effect repeat?
 - b. A NOAEL for the bone marrow toxicity
 - c. Is the effect reversible, progressive or self-limiting?
2. QTc prolongation. This appeared inconsistently. A consistent feature of the QTc evaluation was the lack of detail as to the determination of ECG collection relative to dosing. Also, Bazett's formula appeared to be the only method of correction used, even though it was inappropriate given the heart rates of the dogs. In the acute cardiovascular safety study, there were no apparent effects on QTc. A 2-week, repeat dose study in dogs also showed no QTc effects. A one-month, oral dosing study showed QTc increased in all groups including controls. One month of intravenous dosing showed a decrease in QTc values. A 3-month, oral study showed inconsistent QTc increases from week 4 onward. A HERG assay indicated that nebivolol inhibits the IKr channel with an $IC_{50} = 3 \times 10^{-7} M$ compared to astemizole, $IC_{50} = 2 \times 10^{-8} M$ in the same assay.

3. Endocrine disruption. This conclusion of endocrine disruption is due to several points of data:
- a. Dose-related increase in Leydig cell tumors (LCT) in mice. The LCT were assessed by the Executive CAC to be drug-related. LCT in mice are typically due to an estrogen receptor mechanism.
 - b. Several toxicology studies report weight effects in the reproductive organs of both sexes. Gross and histologic changes were also noted in report texts, but detailed descriptions and incidences were not provided. For the female reproductive tract, the sponsor notes "a more resting aspect in the female genital tract" as well as fewer corpora lutea and more atretic follicles. Changes in the male reproductive organs were noted in the 3-month study in mice and included Leydig cell hyperplasia (160 mg/kg), large nucleated tubular cells and testicular atrophy due to delayed maturation. Rat studies showed increased gonad weight (no detail as to the specifics). The 6-month rat study reported a decrease in gonad weight and testicular degenerative changes with low numbers of spermatozoa and "possible cellular debris in the epididymus." The one-month dog study showed an increase in male prostate weight and no histopath information. The 3-month dog study showed increased gonad weight at 2.5, 10 and 40 mg/kg with urolithiasis at the LD and prostatitis at the MD.

Labeling: Dr. Hausner included labeling recommendations in her review.

Dr. Elizabeth Hausner; January 4, 2005

This review was of the sponsor's November 12, 2004 submission which included 6 studies for review. Two studies were reviewed. In her review of XBL study # 04683, XBL report #RPT01128 *In vitro* Metabolism of [¹⁴C]-Nebivolol in Liver Microsomes, and Liver s9 Fraction from Mouse, Rat, Dog, and Human, Dr. Hausner concluded that overall, the in vitro metabolic profiles of [¹⁴C]-d and [¹⁴C]-l-nebivolol were qualitatively similar. In her review of XBL study #04685, XBL report #RPT01174 Search and Investigation of Nebivolol Metabolites in Plasma Samples from Human, Rat, Mouse, and Dog using Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) techniques, Dr. Hausner stated that the study was initiated several months into the NDA review and completed late in the review cycle. Dr. Hausner stated that this material does not substantially alter the overall non-clinical picture of nebivolol.

Dr. Elizabeth Hausner; December 30, 2004

This review was of the sponsor's November 23, 2004 submission which was a follow-up to a teleconference between the Division and the sponsor in September 2004 when the sponsor was notified that the Executive CAC had determined that the Leydig cell tumors present in mice were drug related. At that teleconference, the sponsor was asked to make a case that this finding was not clinically relevant. This submission included a reevaluation of the slides in a "blinded" fashion and a report from the Pathology Working Group which was assembled after the reread. Dr. Hausner stated that the submission did not change the conclusion of the tumorigenic potential of the drug and the material

presented did not address the Division's question as to the relevance of this finding in humans.

Statistical Review of Carcinogenicity

Ms. Jasmine Choi; July 22, 2004

Ms. Choi reviewed two carcinogenicity studies, a two year rat study (Study 1968) and an 18 month mouse study (Study 1967). Ms. Choi noted that in the rat study the dose-mortality trend tests and homogeneity test for both genders showed no statistically significant treatment effect on survival and that the study had been extended until 50% mortality was reached. Ms. Choi concluded that based on the statistical criteria there were a sufficient number of rats living long enough to present late developing tumors and the high dose reached the MTD. Ms. Choi stated that in the mouse study the treatment did not effect the survival of either gender. Leydig cell tumors in the testis showed a statistically significant trend in males. There were no other tumors with a positive dose-related trend. The validity of the study was evaluated since there were no significant tumor findings in females. Ms. Choi stated that the evaluation suggested that enough numbers of animals were at risk for a sufficient length of time, but that the high dose did not reach the MTD.

Executive CAC Report from meeting on August 24, 2004

The committee found the rat and mouse studies were adequate. The Leydig cell tumors seen in male mice were considered drug-related. The committee also stated that because of the possibility of body weight effects in the rat study altering the tumor incidence in the HD groups, it was requested that the mammary tumors be reanalyzed omitting the HD group. The reanalysis consisted of a trend test comparing the vehicle control, LD and MD groups but omitting the HD group. Benign (adenomatous) neoplasia was to be analyzed separately from carcinoma/sarcoma neoplasms. A combination of all mammary tumors would then also be analyzed. The rat study was found to be negative for carcinogenicity when associated tumor types were analyzed separately. When mammary neoplasms were reanalyzed in accordance with the recommendations of the committee, neither trend tests (vehicle control, LD, and MD) nor pairwise comparisons (vehicle control vs MD) resulted in statistically significant findings.

Chemistry Reviews

Dr. Ramsharan Mittal; November 30, 2007

Dr. Mittal recommends approvable from a CMC perspective because of the withhold status of drug substance manufacturing site at Janssen Pharmaceutica N V, Beerse, BE.

Dr. Ramsharan Mittal; November 1, 2007

Dr. Mittal recommends approval if the pending cGMP inspection of the Jansen manufacturing facility is deemed acceptable. In sum, an expiration date of 36 months is acceptable and Dr. Mittal's recommendations have been incorporated in the draft labeling.

Dr. Ramsharan Mittal; April 29, 2005

Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of _____ months is acceptable for Nebivolol Tablets packaged in _____ bottles of _____ 30, 100 _____ tablets and unit-dose _____.

_____. In addition, the deficiencies noted in earlier CMC reviews have been satisfactorily addressed by the sponsor and the application can be approved from a chemistry perspective.

Dr. Mittal states that the sponsor should be informed to use the following recently approved nebivolol hydrochloride USAN chemical name in the package insert, which should be included in marked up labeling:

1RS,1'RS)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride

Dr. Mittal also noted that the Office of Clinical Pharmacology and Biopharmaceutics review is still pending.

Dr. Ramsharan Mittal; March 11, 2005

Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of _____ months is acceptable for Nebivolol Tablets packaged in _____ bottles of _____ 30, 100 _____ tablets and unit-dose _____.

_____. However, Dr. Mittal states that the chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the Nebivolol 2.5, 5, and 10 mg Tablets. The application is approvable from chemistry perspective pending resolution of these deficiencies.

Dr. Mittal had the following comments for the sponsor:

1. Regarding water and identification specifications of Nebivolol Hydrochloride Tablets

The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about _____. The proposed limit for water content _____ is too high and should be Not More Than _____. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Regarding in-process blend uniformity testing

Please note that mere generation of acceptable data from a number of batches will not be considered a sufficient justification for deletion of in-process blend uniformity testing.

3. Regarding Post-approval Stability Protocols of Nebivolol Hydrochloride Tablets

The post approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on post approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations and should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

4. Regarding labeling issues of the drug product Nebivolol Hydrochloride Tablets

Please submit a request for a USAN for (\pm) nebivolol hydrochloride and provide a copy of the USAN request to this NDA as a part of your response. Please note that the current USP

Dictionary lists only nebivolol free base with inadequate structure representation since no stereochemistry is shown.

Dr. Ramsharan Mittal; February 15, 2005

Dr. Mittal states that the Chemistry Manufacturing and Controls information in this application was provided for - different dose strengths — 2.5, 5, 10, — mg. The sponsor is marketing — dose strengths 2.5, 5, and 10 mg. ? —

In his review, Dr. Mittal states that the chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the nebivolol 2.5, 5, and 10 mg Tablets. Dr. Mittal states the following deficiencies should be included in the action letter:

1. Regarding water and identification specifications of Nebivolol Hydrochloride tablets.

The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about —. The proposed limit for water content of — is too high and should be Not More Than —. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Regarding in-process blend uniformity testing.

Please note that mere generation of acceptable data from a number of batches will not be considered a sufficient justification for deletion of in-process blend uniformity testing.

3. Regarding Post-approval Stability Protocols of Nebivolol Hydrochloride Tablets.

The post approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on post approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations and should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

4. Regarding labeling issues of the drug product Nebivolol Hydrochloride Tablets.

Based on the submitted stability data, an expiration date of — months is acceptable for neбиволol tablets packaged in — bottles of 30, 100, — tablets and unit-dose

Dr. Mittal stated that a final recommendation on approvability of Nebivolol Hydrochloride 2.5, 5, and 10 mg Tablets can not be given at this time since an overall recommendation from the Office of Compliance is pending because cGMP inspection of the drug substance manufacturing facilities (Jansen Pharmaceuticals) has not been completed and the facilities are scheduled to be inspected between February 6 – 16, 2005.

EES: Pending, due to be completed February 16, 2004

Methods of Validation: To be submitted after NDA approval

Labeling: Dr. Mittal included labeling recommendations in his review.

Categorical Exclusion from the Environmental Assessment: Acceptable

DDMAC Reviews

In a review dated October 29, 2007, DDMAC reviewed the proposed package insert (from October 27, 2007). DDMAC offered recommendations to the Clinical Pharmacology, Clinical Studies, Warnings, Precautions, and Adverse Reactions sections of the PI.

In a review dated March 10, 2005, DDMAC reviewed the sponsor's rebuttal to DDMAC's objection to the use of the tradename ' ——— . DDMAC stated that they continue to consider the tradename overly fanciful and overstating the efficacy of nebivolol.

In a review dated February 9, 2005, DDMAC provided comments on the sponsor's proposed package insert.

DMETS Reviews

DMETS; November 16, 2007

In a review dated November 16, 2007, DMETS concurred with DDMAC to NOT recommend the use of the proprietary name ——— based on promotional concerns.

DMETS; October 18, 2007

In a review dated October 18, 2007, DMETS did NOT recommend the use of the proprietary name Cirmaxen. DDMAC found Cirmaxen to be acceptable from a promotional perspective. In November, the sponsor submitted three more tradenames for DMETS to consider including ——— , 2) Bystolic, ——— .

DMETS; February 3, 2005

In a review dated February 3, 2005, DMETS did not recommend the use of the proprietary name ——— and commented also that DDMAC did not recommend the use of ——— from a promotional perspective.

DMETS; August 11, 2004

In a review dated August 11, 2004, DMETS provided comments on the sponsor's original draft labels and labeling submitted by the sponsor without a proprietary name. DMETS requested final printed labeling be submitted for review when available.

ACTION:

An approvable (AE) letter has been drafted for Dr. Temple's review.

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/s/

Dan Brum
12/11/2007 12:59:21 PM
CSO

11/16/07



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 16, 2007

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Thru: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Hoquist, RPh, Director
Division of Medication Errors and Technical Support

From: Diane C. Smith, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

Subject: Proprietary Name Review

Drug Name(s):
(Nebivolol Hydrochloride) Tablets

Application Type/Number: NDA 21-742

Applicant/sponsor: Mylan/Bertek Pharmaceuticals, Inc.

OSE RCM #: 2007-2291

1 INTRODUCTION

This memorandum is written in response to a November 2, 2007, request from the Division of Cardiovascular and Renal Products for review of the proprietary name _____ NDA 21-742.

1.1 PRODUCT DESCRIPTION

_____ (nebivolol hydrochloride) is a competitive and selective β 1-adrenergic (cardioselective) receptor antagonist indicated for the management of hypertension. The usual dose is 5 mg to 10 mg daily. _____ will be supplied as 2.5 mg, 5 mg and 10 mg oral tablets.

2 DISCUSSION

During the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommend the use of the proposed proprietary name _____ from a promotional perspective because the name overstates the efficacy of the drug product DDMAC provided the following statement:

2.1 _____ (PRIMARY NAME)

DDMAC objects to the proposed trade name _____ because it overstates the efficacy of the drug product by misleadingly implying it is superior over other medications indicated for the treatment of hypertension. _____ easily invokes the word _____. Therefore, the proposed trade name suggests that this product _____ is somehow superior to other treatment options for hypertension. In the absence of substantial evidence or substantial clinical experience to support such an advantage over other treatment options for hypertension, the proposed trade name is misleading.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

3 CONCLUSION AND RECOMMENDATIONS

As per email correspondence with the Division of Cardiovascular and Renal Products on November 5, 2007 the Division concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name _____, since the Division supports DDMAC's objection to the name based on promotional concerns. We recommend the sponsor be notified of the decision to object to the name based on promotional concerns and advise the sponsor that DMETS will proceed in reviewing the secondary and tertiary proposed names submitted by the sponsor. Additionally, the revised labels and labeling submitted by the sponsor will be reviewed in a separate review.

If you have any questions for DDMAC, please contact the regulatory review officer, Carrie Newcomer, at 301-796-1233. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. If you have any other questions or need clarification, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

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/s/

Diane Smith
11/16/2007 02:51:13 PM
CSO

Todd Bridges
11/16/2007 02:52:01 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/16/2007 02:55:11 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/16/2007 04:32:01 PM
DRUG SAFETY OFFICE REVIEWER

3 Page(s) Withheld

 Trade Secret / Confidential

 b Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

6/1/05

Project Manager Overview
NDA 21-742
Nebivolol Tablets

Overview:

Bertek Pharmaceuticals submitted a New Drug Application (NDA) for Nebivolol Hydrochloride — 2.5, 5, 10, and — tablets on April 30, 2004. The data submitted is to support an indication for the use of nebivolol in the management of hypertension when used alone or in combination with other antihypertensive agents.

Division Director's Memo

Dr. Norman Stockbridge; May 9, 2005

Dr. Stockbridge supported an approvable action for this NDA and briefly discusses efficacy results and issues of concern.

Secondary Review

Dr. Abraham Karkowsky; February 23, 2005

Dr. Karkowsky outlined the rationale for an approvable recommendation for Nebivolol Tablets for the treatment of hypertension. In his review, he states that there is sufficient information to ensure that nebivolol at a dose range of to 40 mg once daily is effective in the treatment of essential hypertension. In addition, he stated that there is adequate information that nebivolol is useful for the treatment of hypertension in both Caucasian and black patients. However, Dr. Karkowsky stated that an approval recommendation will be dependant on demonstrating that the Leydig cell tumors observed in male mice at a dose of 40 mg/kg are not a relevant risk to humans.

Medical Review

Dr. Karen Hicks, Dr. Juan Carlos Pelayo, Dr. Katherine Lille, Dr. Maryann Gordon, and Dr. Shari Targum; April 22, 2005

This review was of all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the pivotal studies. Per Dr. Hicks, this review is identical to the review dated April 11, 2005 with minor editorial changes. Therefore, only this copy is included in the action package.

Dr. Karen Hicks, Dr. Juan Carlos Pelayo, Dr. Katherine Lille, Dr. Maryann Gordon, and Dr. Shari Targum; April 11, 2005

NOTE: This review was revised and is dated April 22, 2005. This version is not included in the action package.

This review was of all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the pivotal studies.

Dr. Salma Lemtouni; March 10, 2005

In her review of safety, Dr. Lemtouni stated that the clinical program was designed to evaluate the efficacy of nebivolol and, as a result, was underpowered to assess the association of nebivolol with many of the adverse events observed. Dr. Lemtouni states that her conclusions drawn with regard to the safety of nebivolol rely on the comparison of safety results from the review of carvedilol, the labels of carvedilol and metoprolol succinate, and on the foreign post marketing data of nebivolol.

Dr. Lemtouni concluded that adverse events known to be associated with beta-adrenergic antagonism were experienced by subjects exposed to nebivolol as expected. Abnormalities in liver function tests were observed with nebivolol as they were with carvedilol in hypertensive patients. Chest pain was experienced at a similar incidence as with metoprolol succinate in hypertensive patients. Dr. Lemtouni believed that Nebivolol may not be the only beta-blocker to be associated with potential angioedema because events of angioedema were reported in post marketing experience with many other beta-blockers. Therefore, the general experience of the nebivolol study population with regard to study drug adverse effects was not different from that of the carvedilol and metoprolol hypertension study populations.

Dr. Lemtouni recommended including a warning in the label about potential angioedema.

Per Dr. Lemtouni, this review is an updated version of her previous review dated February 9, 2005 and is therefore the only version included in the action package.

Dr. Salma Lemtouni; February 9, 2005

NOTE: This review was revised by Dr. Lemtouni and is dated March 10, 2005. This version is not included in the action package.

In her review of safety, Dr. Lemtouni stated that the clinical program was designed to evaluate the efficacy of nebivolol and, as a result, was underpowered to assess the association of nebivolol with many of the adverse events observed. Dr. Lemtouni states that her conclusions drawn with regard to the safety of nebivolol rely on the comparison of safety results from the review of carvedilol, the labels of carvedilol and metoprolol succinate, and on the foreign post marketing data of nebivolol.

Dr. Lemtouni noted some issues that are of concern to her: nebivolol's potential myocardial ischemic effect, its lipid metabolism effects, its seemingly compromising effect of renal function, and its potential interaction with alcohol.

Dr. Karen Hicks; January 31, 2005

In her review of efficacy, Dr. Hicks stated that nebivolol is approvable for the treatment of _____ hypertension, pending the following results:

1. The sponsor plans to perform mechanistic studies in mice and rats to explain the development of Leydig cell tumors (LCT). If the sponsor proves nebivolol is not potentially carcinogenic in humans, the application is approvable.
2. Through consultative review, the Division of Reproductive and Urologic Drug Products (DRUDP) will assist the Cardio-Renal Division in identifying the most sensitive markers for drug-related estrogenic effects in humans and in determining whether or not these markers predict the development of subsequent malignancies.

Dr. Hicks believes that based on the mouse carcinogenicity findings, nebivolol may be carcinogenic in humans. She stated that there is some nebivolol safety data covering approximately two years, but believes this time period does not adequately evaluate nor predict the malignant potential of this drug which would be taken chronically. In addition, Dr. Hicks states that it is unlikely post-marketing surveillance in Europe, where nebivolol has already been approved, would adequately record all malignancies in patients taking nebivolol.

Dr. Hicks states that the primary efficacy endpoint was the change in mean trough sitting diastolic blood pressure at the end of treatment compared to baseline. Nebivolol showed statistically significant results at doses of 1.25 to 40 mg in NEB-302; 5, 10, and 20 mg in NEB-305; and 5 to 40 mg in NEB-202. In addition, nebivolol had a statistically significant effect on most of the secondary endpoints.

In her review, Dr. Hicks stated that nebivolol is not significantly different from other β_1 selective blockers currently on the market, except that it is potentially carcinogenic in humans. Blacks require higher doses of nebivolol for efficacy, as they do with other beta blockers. Although *in vitro* experiments using human umbilical vein preparations and forearm blood flow studies in small numbers of humans suggest nebivolol may have some effect on nitric oxide release, the exact mechanism is unknown. Metoprolol, another β_1 selective adrenoceptor blocking agent, also increases nitric oxide release. Many of the studies were not placebo-controlled and were performed up to seventeen years ago. With technological improvements, it is unclear whether or not these results are reproducible today.

Dr. Hicks stated that risk management activities will be dependant on the findings of the mechanistic studies which the sponsor plans to perform and recommendations from the DRUDP.

Financial Disclosure: In her review, Dr. Hicks noted that the sponsor included Financial Certifications (FDA Form 3454) for the investigator's participating in NEB-302, NEB-305, NEB-202, NEB-306, NEB-203, and NEB-321. The sponsor stated that no investigator or sub-investigator had financial interest as described in 21 CFR 54 that required financial disclosure.

Labeling: Dr. Hicks stated in her review, that a labeling review is pending the Agency's final decision regarding approvability.

Clinical Inspection

In a review dated February 15, 2005, the Division of Scientific Investigation stated that no major deficiencies were noted in the three sites inspected that could compromise the integrity of the data and concluded that the data reviewed is acceptable. No subsequent actions or follow up inspections were recommended. There were no limitations to the inspections.

Statistical Review

Ms. Jasmine Choi; December 17, 2004

Ms. Choi concluded in her review that nebivolol had a statistically significant effect on reducing sitting diastolic blood pressure not only in non-black patients, but also in black patients. The secondary analyses on other primary efficacy measurements confirmed that nebivolol had a statistically significant antihypertensive effect on mild to moderate hypertension population.

The primary analyses on general population (NEB-302 and NEB-305) showed that the sitting DBP of all dosed groups was significantly decreased compared to the placebo groups (NEB-302, $p < 0.0001$ for all doses; NEB-305, $p < 0.0015$). The same analysis on black population (NEB-202) showed a statistically significant reduction of sitting DBP in all dose groups, except the 2.5 mg dose group.

For the secondary analyses, change of sitting SBP at trough and rates of responder, which was defined as a patient whose average sitting DBP at trough was either < 90 mmHg at the end of treatment or had decreased by ≥ 10 mmHg from baseline, were analyzed. The results of these secondary analyses confirmed the findings from the primary analyses.

Clinical Pharmacology and Biopharmaceutics

Dr. Elena Mishina; May 11, 2005

In her review, Dr. Mishina reviewed the sponsor's responses to the comments that were sent by the Division following the first clinical pharmacology and biopharmaceutics review. The following dissolution methods and specifications were recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	<u> </u> in 30 minutes

Dr. Elena Mishina and Dr. Robert Kumi; January 31, 2005

In this review, Dr. Mishina and Dr. Kumi stated that the clinical pharmacology and biopharmaceutics sections are acceptable, provided that the labeling comments are adequately addressed. The biowaiver requested for the 2.5 mg dose was granted. In addition, the following dissolution methods and specifications were recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	—— in 15 minutes

The following list of issues was not addressed by the sponsor:

1. The pharmacokinetics of the active metabolites of nebivolol was not assessed. This led to the inability to explain why the striking difference in pharmacokinetics of the parent drug in extensive and poor metabolizers of CYP2D6 did not show any differences in the drug effect.
2. The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.
3. The sponsor is requested to evaluate the PK/PD relationship in African-American hypertensive patients.

Labeling: Dr. Mishina and Dr. Kumi included labeling recommendations in their review.

Pharmacology Review

Dr. Elizabeth Hausner; April 11, 2005

This review was of a protocol change of the sponsor's mechanistic study which the sponsor had designed to provide support to their assertion that nebivolol did not pose a cancer risk to humans. The Division agreed with the sponsor's proposed change to the protocol and conveyed this information to them.

Dr. Elizabeth Hausner; April 11, 2005

This review was of summary tables of the incidences of the histological findings which were requested by the Division in order to clarify various references throughout the reports that indicated that the reproductive tract was one of the target organs of toxicity. Dr. Hausner stated that she is unable to come to a definitive interpretation of the data, but the data generates the overall impression that there is a signal to be investigated regarding a possible hormonal effect of nebivolol.

Dr. Elizabeth Hausner; March 24, 2005

This review was of material submitted from a DMF and was in response to the chemistry reviewer noting that there was an impurity to be qualified. The sponsor provided studies in support of the qualification of the impurity. Dr. Hausner stated that overall, the combination of impurities added to nebivolol did not cause any new effects compared to nebivolol alone. She stated that there is no discernible signal that this combination of impurities and nebivolol causes any appreciable biological effects.

Dr. Hausner noted in her review, that the sponsor stated that there is a drug-related effect on cyclicity seen at 14 days of dosing using a dose that has not produced clear effects after 6 months of dosing.

Dr. Elizabeth Hausner; February 24, 2005

This review covered material submitted by the sponsor in response to the Division's repeated requests for data to indicate that the reproductive toxicology findings were not of clinical relevance. Dr. Hausner concluded that this submission did adequately address the reproductive and developmental issues that concern the Division.

Dr. Elizabeth Hausner; January 24, 2005

In her review, Dr. Hausner stated that this application was approvable depending upon the clinical findings. Dr. Hausner recommended the following nonclinical studies, but added that at this stage there may be sufficient clinical data to resolve these issues without conducting further non-clinical testing: characterization of the active metabolites, possible bone marrow toxicity, endocrine disruption, and repolarization effects. Dr. Hausner concluded that there are a number of consistent features in the toxicology studies. She stated that the level of detail provided is sub-optimal, particularly with regard to histopathology results. In the majority of reports, summary incidence tables are lacking and a scoring system is used which she believes to some extent makes interpretation difficult. Dr. Hausner added that detailed verbal descriptions of histopathology findings are almost entirely lacking. Similar comments could be made about some of the safety pharmacology studies where raw or interpretable results were not presented and scoring systems were used, making independent interpretation difficult. Dr. Hausner noted that reproductive toxicology was apparent. Dr. Hausner noted the following unresolved toxicology issues:

1. N122168 Micronucleus test in mice: single oral dose. Single oral doses of nebivolol in male and female mice showed significant ($p \leq 0.05-0.001$) and dose-related reduction in bone marrow proliferation at the 24 hour sampling time. This bone marrow toxicity was not examined or at least there was no information in the toxicology reports characterizing or further exploring this finding. Decreases in HCT, Hb and RBC were seen in the hematology results of most toxicology studies. Enlarged spleens with increased RBC in the pulp were reported for most studies, even in situations where hematology changes were not apparent. The

findings are more consistent with a hemolytic anemia rather than bone marrow depression. Dr. Hausner was unsure if the original observation was a random fluke, as one would think that if the observation was real, that there might have been some clinical evidence to corroborate this finding by now. The points which should have been characterized include:

- a. Did the original effect repeat?
 - b. A NOAEL for the bone marrow toxicity
 - c. Is the effect reversible, progressive or self-limiting?
2. QTc prolongation. This appeared inconsistently. A consistent feature of the QTc evaluation was the lack of detail as to the determination of ECG collection relative to dosing. Also, Bazett's formula appeared to be the only method of correction used, even though it was inappropriate given the heart rates of the dogs. In the acute cardiovascular safety study, there were no apparent effects on QTc. A 2-week, repeat dose study in dogs also showed no QTc effects. A one-month, oral dosing study showed QTc increased in all groups including controls. One month of intravenous dosing showed a decrease in QTc values. A 3-month, oral study showed inconsistent QTc increases from week 4 onward. A HERG assay indicated that nebivolol inhibits the IKr channel with an $IC_{50}=3 \times 10^{-7} M$ compared to astemizole, $IC_{50}=2 \times 10^{-8} M$ in the same assay.
3. Endocrine disruption. This conclusion of endocrine disruption is due to several points of data:
- a. Dose-related increase in Leydig cell tumors (LCT) in mice. The LCT were assessed by the Executive CAC to be drug-related. LCT in mice are typically due to an estrogen receptor mechanism.
 - b. Several toxicology studies report weight effects in the reproductive organs of both sexes. Gross and histologic changes were also noted in report texts, but detailed descriptions and incidences were not provided. For the female reproductive tract, the sponsor notes "a more resting aspect in the female genital tract" as well as fewer corpora lutea and more atretic follicles. Changes in the male reproductive organs were noted in the 3-month study in mice and included Leydig cell hyperplasia (160 mg/kg), large nucleated tubular cells and testicular atrophy due to delayed maturation. Rat studies showed increased gonad weight (no detail as to the specifics). The 6-month rat study reported a decrease in gonad weight and testicular degenerative changes with low numbers of spermatozoa and "possible cellular debris in the epididymus." The one-month dog study showed an increase in male prostate weight and no histopath information. The 3-month dog study showed increased gonad weight at 2.5, 10 and 40 mg/kg with urolithiasis at the LD and prostatitis at the MD.

Labeling: Dr. Hausner included labeling recommendations in her review.

Dr. Elizabeth Hausner; January 4, 2005

This review was of the sponsor's November 12, 2004 submission which included 6 studies for review. Two studies were reviewed. In her review of XBL study # 04683, XBL report #RPT01128 *In vitro* Metabolism of [¹⁴C]-Nebivolol in Liver Microsomes, and Liver s9 Fraction from Mouse, Rat, Dog, and Human, Dr. Hausner concluded that overall, the *in vitro* metabolic profiles of [¹⁴C]-d and [¹⁴C]-l-nebivolol were qualitatively similar. In her review of XBL study #04685, XBL report #RPT01174 Search and Investigation of Nebivolol Metabolites in Plasma Samples from Human, Rat, Mouse, and Dog using Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) techniques, Dr. Hausner stated that the study was initiated several months into the NDA review and completed late in the review cycle. Dr. Hausner stated that this material does not substantially alter the overall non-clinical picture of nebivolol.

Dr. Elizabeth Hausner; December 30, 2004

This review was of the sponsor's November 23, 2004 submission which was a follow-up to a teleconference between the Division and the sponsor in September 2004 when the sponsor was notified that the Executive CAC had determined that the Leydig cell tumors present in mice were drug related. At that teleconference, the sponsor was asked to make a case that this finding was not clinically relevant. This submission included a reevaluation of the slides in a "blinded" fashion and a report from the Pathology Working Group which was assembled after the reread. Dr. Hausner stated that the submission did not change the conclusion of the tumorigenic potential of the drug and the material presented did not address the Division's question as to the relevance of this finding in humans.

Statistical Review of Carcinogenicity

Ms. Jasmine Choi; July 22, 2004

Ms. Choi reviewed two carcinogenicity studies, a two year rat study (Study 1968) and an 18 month mouse study (Study 1967). Ms. Choi noted that in the rat study the dose-mortality trend tests and homogeneity test for both genders showed no statistically significant treatment effect on survival and that the study had been extended until 50% mortality was reached. Ms. Choi concluded that based on the statistical criteria there were a sufficient number of rats living long enough to present late developing tumors and the high dose reached the MTD. Ms. Choi stated that in the mouse study the treatment did not effect the survival of either gender. Leydig cell tumors in the testis showed a statistically significant trend in males. There were no other tumors with a positive dose-related trend. The validity of the study was evaluated since there were no significant tumor findings in females. Ms. Choi stated that the evaluation suggested that enough numbers of animals were at risk for a sufficient length of time, but that the high dose did not reach the MTD.

Executive CAC Report from meeting on August 24, 2004

The committee found the rat and mouse studies were adequate. The Leydig cell tumors seen in male mice were considered drug-related. The committee also stated that because

of the possibility of body weight effects in the rat study altering the tumor incidence in the HD groups, it was requested that the mammary tumors be reanalyzed omitting the HD group. The reanalysis consisted of a trend test comparing the vehicle control, LD and MD groups but omitting the HD group. Benign (adenomatous) neoplasia was to be analyzed separately from carcinoma/sarcoma neoplasms. A combination of all mammary tumors would then also be analyzed. The rat study was found to be negative for carcinogenicity when associated tumor types were analyzed separately. When mammary neoplasms were reanalyzed in accordance with the recommendations of the committee, neither trend tests (vehicle control, LD, and MD) nor pairwise comparisons (vehicle control vs MD) resulted in statistically significant findings.

Chemistry Review

Dr. Ramsharan Mittal; April 29, 2005

Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of — months is acceptable for Nebivolol Tablets packaged in — bottles of — 30, 100 — tablets and unit-dose — . In addition, the deficiencies noted in earlier CMC reviews have been satisfactorily addressed by the sponsor and the application can be approved from a chemistry perspective.

Dr. Mittal states that the sponsor should be informed to use the following recently approved nebivolol hydrochloride USAN chemical name in the package insert, which should be included in marked up labeling:

1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride

Dr. Mittal also noted that the Office of Clinical Pharmacology and Biopharmaceutics review is still pending.

Dr. Ramsharan Mittal; March 11, 2005

Dr. Mittal states that an acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of — months is acceptable for Nebivolol Tablets packaged in — bottles of — 30, 100 — tablets and unit-dose — . However, Dr. Mittal states that the chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the Nebivolol 2.5, 5, and 10 mg Tablets. The application is approvable from chemistry perspective pending resolution of these deficiencies.

Dr. Mittal had the following comments for the sponsor:

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1. Regarding water and identification specifications of Nebivolol Hydrochloride Tablets

The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about —. The proposed limit for water content — is too high and should be Not More Than —. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Regarding in-process blend uniformity testing

Please note that mere generation of acceptable data from a number of batches will not be considered a sufficient justification for deletion of in-process blend uniformity testing.

3. Regarding Post-approval Stability Protocols of Nebivolol Hydrochloride Tablets

The post approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on post approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations and should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

4. Regarding labeling issues of the drug product Nebivolol Hydrochloride Tablets

Please submit a request for a USAN for (\pm) nebivolol hydrochloride and provide a copy of the USAN request to this NDA as a part of your response. Please note that the current USP

Dictionary lists only nebivolol free base with inadequate structure representation since no stereochemistry is shown.

Dr. Ramsharan Mittal; February 15, 2005

Dr. Mittal states that the Chemistry Manufacturing and Controls information in this application was provided for different dose strengths — 2.5, 5, 10, and — mg. The sponsor is marketing — dose strengths 2.5, 5, and 10 mg. —

In his review, Dr. Mittal states that the chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the nebivolol 2.5, 5, and 10 mg Tablets. Dr. Mittal states the following deficiencies should be included in the action letter:

1. Regarding water and identification specifications of Nebivolol Hydrochloride tablets.

The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about —. The proposed limit for water content — is too high and should be Not More Than —. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Regarding in-process blend uniformity testing.

Please note that mere generation of acceptable data from a number of batches will not be considered a sufficient justification for deletion of in-process blend uniformity testing.

3. Regarding Post-approval Stability Protocols of Nebivolol Hydrochloride Tablets.

The post approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on post approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations and should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

4. Regarding labeling issues of the drug product Nebivolol Hydrochloride Tablets.

Based on the submitted stability data, an expiration date of ~ months is acceptable for nebivolol tablets packaged in ~ bottles of ~30, 100 ~ tablets and unit-dose

Dr. Mittal stated that a final recommendation on approvability of Nebivolol Hydrochloride 2.5, 5, and 10 mg Tablets can not be given at this time since an overall

recommendation from the Office of Compliance is pending because cGMP inspection of the drug substance manufacturing facilities (Jansen Pharmaceuticals) has not been completed and the facilities are scheduled to be inspected between February 6 – 16, 2005.

EES: Pending, due to be completed February 16, 2004

Methods of Validation: To be submitted after NDA approval

Labeling: Dr. Mittal included labeling recommendations in his review.

Categorical Exclusion from the Environmental Assessment: Acceptable

DDMAC Review

In a review dated March 10, 2005, DDMAC reviewed the sponsor's rebuttal to DDMAC's objection to the use of the tradename _____. DDMAC stated that they continue to consider the tradename overly fanciful and overstating the efficacy of nebivolol.

In a review dated February 9, 2005, DDMAC provided comments on the sponsor's proposed package insert.

DMETS Review

In a review dated February 3, 2005, DMETS did not recommend the use of the proprietary name _____ and commented also that DDMAC did not recommend the use of _____ from a promotional perspective.

In a review dated August 11, 2004, DMETS provided comments on the sponsor's original draft labels and labeling submitted by the sponsor without a proprietary name. DMETS requested final printed labeling be submitted for review when available.

Action:

An approvable letter has been drafted.

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/s/

Melissa Robb

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CSO

Minutes of Telecon

Date of telecon: December 15, 2004

Mylan Bertek Attendees

Andrea Miller, R.Ph. Esq. Vice President, Regulatory Affairs
John O'Donnell, Ph.D., Chief Scientific Officer
Jeff Smith, Ph.D. Assistant Director, Pharmacology and Toxicology
Jim Sherry, M.D., Ph.D., Medical Director
Bruce Bottini, Pharm D. , Executive Director, Drug Safety
Betty Riggs, M.D., Vice President, Clinical Research
Kelly Tate, M.S., Director, Regulatory Affairs

FDA Attendees:

Karen Hicks, M.D. Medical Officer
Elizabeth Hausner, D.V.M., Pharmacologist
Al DeFelice, Ph.D., Supervisory Pharmacologist
Chair: E. Hausner

To resolve the question of the relevance of the Leydig cell tumors seen in mice, the Division is recommending either a discussion in front of the full Carcinogenicity Assessment Committee or preferably, mechanistic studies. The Division feels that generation of compound-specific data may be of more value than asking for debate based on opinion.

Based upon references provided by the sponsor, it is recommended that design of a study protocol include both rats and mice for comparative purposes and thorough histological examination of those tissues and locations in tissues most likely to be affected by an endocrine mechanism. Use of an appropriate positive control is also necessary for a valid study.

The other issue discussed was in regard to histology from the toxicology reports and the findings of the reproductive and developmental studies, points raised by the Division in 2002. The sponsor was reminded of various statements made by the original authors regarding the reproductive tract as a target organ of toxicity, disruption of steroid metabolism and the lack of supporting detail for these statements. The presentation of histopathology in the study reports also did not allow for independent interpretation of the above statements. The Division would like the sponsor to clarify the various statements made in the study reports and to provide incidence tables of the relevant histological findings in a form that allows for independent interpretation of the data.

The Sponsor replied that they were also considering the utility of a mechanistic study for nebivolol and have been examining possible contract sites. A draft protocol and timeline will be provided to the Division within the next week for discussion.

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this page is the manifestation of the electronic signature.

/s/

Elizabeth Hausner
5/11/05 11:33:01 AM
PHARMACOLOGIST
Elizabeth Hausner

Albert Defelice
5/13/05 03:34:14 PM
PHARMACOLOGIST

4/28/05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

Mylan Bertek Pharmaceuticals Inc.
Attention: Andrea B. Miller, R.Ph., Esq.
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26505

Dear Dr. Miller:

We acknowledge receipt on April 13, 2005 of your April 12, 2005 correspondence notifying the Food and Drug Administration that the corporate name has been changed from

Bertek Pharmaceuticals Inc.

to

Mylan Bertek Pharmaceuticals Inc.

for NDA 21-742 for Nebivolol Hydrochloride Tablets, 2.5, 5 and 10 mg.

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Room 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research